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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,231	01/18/2001	Deborah J. Phippard	3221-US	7382

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PHARMACIA CORPORATION
GLOBAL PATENT DEPARTMENT
POST OFFICE BOX 1027
ST. LOUIS, MO 63006

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,231	PHIPPARD ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,11,18,29 and 32-48* is/are pending in the application.

4a) Of the above claim(s) *32-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,5-7,11,18 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 5/13/04. Claims 32-48 were added as requested.

Newly submitted claims 32-48 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 32-48 are drawn methods for identifying osteoarthritis inhibitors by classified in class 435, subclass 7.2. On 9/3/02 Applicant elected without traverse to prosecute an invention drawn to nucleic acids comprising SEQ ID NO:58, and methods of making the encoded protein. Claims 32-48 require use of a cell that has "a receptor for a nucleic acid of SEQ ID NO:58", but the claims do not appear to require SEQ ID NO:58 at all. As such the inventions appear to be unrelated because the nucleic acid has a different function, different effects, and is not disclosed as used in the method. In the event Applicant intended to claim assays in which the recited receptor was encoded by SEQ ID NO:58, the inventions would be related as a product and a process of use. Such inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the nucleic acids could be used for different purposes such as hybridization, or expression of the encoded protein for the purpose of making antibodies. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 32-

48 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 5-7, 11, 18, 29, 32-48 are pending in the application.

Claims 1, 5-7, 11, 18, and 29 are under consideration in this Office Action.

Priority

This application was filed on 01/18/2001.

Priority was claimed to provisional application 60/176,523, filed 01/18/2000.

Drawings

The application contains no drawings.

Rejections Withdrawn

The rejection of claims 1, 6, 7, 11, and 18 under 35 U.S.C. 101 is withdrawn in view of Applicant's amendment adding the word "isolated" to the claims.

The rejection of claims 5-7, 11, and 18 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment deleting "between 90% to 100%".

The rejection of claims 1, 5-7, 11, 18, and 29 under 35 U.S.C. 112, first paragraph for lack of adequate written description is withdrawn in view of Applicant's amendment limiting the claims to an isolated nucleic acid **consisting** of SEQ ID NO:58 or its complement.

Claim Objections

A typographical error was introduced into claim 1 in the Listing of Claims submitted 5/13/04, "compliment" is misspelled.

Claim 1 is objected to because it recites "the group consisting of SEQ ID NO:58, or a compliment [sic] thereof." Due to use of the conjunction "or", the claim recites two groups, each consisting of only a single member. However, a group must consist of more than one member, or it is not a group. Substitution of "and" for "or" is suggested.

Claim 11 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 11 is drawn to a recombinant DNA comprising a nucleic acid of claim 1. However, claim 1 is drawn to an isolated nucleic acid "consisting of" a nucleic acid sequence. The claim uses closed language to describe the nucleic acid. As a result, claim 11 does not further limit the isolated nucleic acid set forth in claim 1, instead, it improperly adds matter ("recombinant DNA") which is not accounted for in claim 1. Because it does not further limit claim 1, but instead broadens it, it is an improper dependent claim.

Claim Interpretation

The term "compliment" in claim 1 is interpreted as "complement", which in turn is interpreted in view of the specification at paragraph 66 as a nucleic acid that is complementary to the entire length of SEQ ID NO:58. Paragraph 66 reads: "[t]he term "complement" means that one nucleic acid exhibits complete complementarity with

another nucleic acid." As such, nucleic acids that are complementary over their entire length to SEQ ID NO:58, but that are shorter or longer than SEQ ID NO:58, are not considered to be embraced by the claim. This is because the duplex that would result from hybridization between such a nucleic acid and SEQ ID NO:58 would necessarily contain at least one unpaired base, and complementarity between the two nucleic acids would not be "complete". As a result no rejection has been made under 35 USC 102 over e.g. a composition comprising all possible isolated oligonucleotide decamers (Brennan et al (US Patent 5,474,796, issued 12/12/95) see column 9, lines 48-55).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1, 5-7, 11, 18, and 29 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 and dependents are drawn to nucleic acids consisting of SEQ ID NO:58 or its complement. The specification teaches that the claimed nucleic acids can be used to diagnose osteoarthritis (OA), to serve as targets for small molecule drug

development, to generate therapeutics directly (i.e. gene therapeutics), and to facilitate cloning the complete gene. See pages 3-8.

Enablement of the use of the claimed polynucleotides as diagnostics for OA, for drug development, or for therapy, depends on the establishment of a relationship between OA and the polynucleotides. SEQ ID NO:58 was identified by data mining of ESTs derived from libraries generated from OA patient tissues and non-OA patient tissues. The specification teaches that SEQ ID NO:58 was "preferentially observed" in libraries generated from OA patient tissues. See e.g. page 3, lines 1-12. It is unclear what is meant by "preferentially observed", and the specification does not disclose sufficient data for one to determine what "preferentially observed" might mean. As a result, the relationship between OA and SEQ ID NO:58 is unclear. For example, "preferentially observed" could mean that SEQ ID NO:58 was never observed in the non-OA libraries, or it could mean that a SEQ ID NO:58 was simply observed less frequently in the non-OA libraries. No data is presented regarding the relative amounts of SEQ ID NO:58 in OA versus non-OA tissues. This is an important point because, as discussed more fully below, in order to use SEQ ID NO:58 as a diagnostic one must obviously know what level of expression of SEQ ID NO:58 is diagnostic of OA. Applicant states at page 9 of the response filed 5/13/04 that "preferentially observed means the ability of a first test compound to preferentially bind to a receptor or other biologically active portion of a second compound as compared to a known compound." This response fails to clarify the issue because it offers no information regarding the extent to which SEQ ID NO:58 was "preferentially observed" in disease versus control

tissues. As a result, such that the relationship between OA and SEQ ID NO:58 remains unclear.

The prior art recognized that comparison and analysis of differentially expressed ESTs from disease-related and normal libraries was an effective means of identifying candidate sequences that could be developed as diagnostics. See e.g. Fannon (TIBS (1996) 14(8): 294-298) who taught that "[c]arefully constructed EST databases can be viewed as a statistical sampling of genes expressed in a variety of tissues, disease states and developmental stages." Fannon continues " The database becomes a decision-support tool that helps identify candidates for more rigorous subsequent characterization". See page 295, column 1, first two paragraphs. Fannon indicates that EST-database approaches can be used to identify a **potential** diagnostic sequence, but adds that there are a number of issues associated with the EST-database approach that need further study, including:

-How much sequencing should be performed on each library for a representative sampling of gene expression, and,

-In view of the fact that expression patterns vary among individuals, among library-preparations methods, and in response to external stimuli, how do we determine what is a 'normal' amount of gene expression?

Fannon points out that "[w]ork is needed to quantify how much variation in gene expression may be considered healthy or normal, and at what point the expression pattern shifts to the 'disease' profile." See page 296, column 2, line 18 to page 297, column 2, line 14. Given these teachings, it is apparent that the raw results of EST-data

mining in disease versus control tissues can provide one with a starting point on the road to the development of a potential diagnostic, if one can show that the sample is statistically significant, if it is determined that the libraries used contain a representative sample of gene expression, and if one has established the threshold between normal and disease-related expression levels in view of the variability of gene expression levels in various patients and differences in library preparation methods. In the instant case, 3 EST libraries were generated from 6 different OA donors (5 cartilage donors and one synovium donor), and were compared to two libraries generated from 5 non-OA donors (4 cartilage donors and one synovium donor). It is unclear how the comparison was made, if the contributions of each donor were equal, and there is no information on the genetic backgrounds of the donors. In view of the small sample size, and the uncertain nature of the library composition, it is extremely unpredictable as to whether the sample is statistically significant and contains a representative sample of gene expression. Furthermore the specification has not established what, if any, amount of SEQ ID NO:58 expression correlates with OA, and what amount is indicative of no disease. So, at best one of skill in the art would view SEQ ID NO:58 as a candidate sequence which could possibly be developed into a diagnostic tool after further research to more rigorously establish a true correlation between its expression and OA. However, the specification fails to provide guidance or working examples information to allow one of skill in the art to assess critical variables related to the preparation of the libraries and the natural variability in expression among individuals, and the specification provides no guidance or working example with regard to what is the threshold between normal

and disease-related expression levels in of any gene in OA. MPEP 608.01(p) states that "[w]hile the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." In this case the specification provides no specific guidance as to what amount of SEQ ID NO:58 expression is considered to be diagnostic.

Similarly, asserted uses including use of the claimed sequences to isolate the full length clone for analysis of the encoded protein, to develop gene-based therapies, and to serve as targets for small molecule drug development also depend on first establishing a significant correlation between SEQ ID NO:58 and OA, or on identifying some other function of SEQ ID NO: 58. In view of the foregoing discussion regarding the lack of a significant correlation between SEQ ID NO:58 and OA, and the fact that the specification discloses no other function for SEQ ID NO:58 (see e.g. Table 1 at page 77), one of skill in the art would have to perform undue experimentation to use the claimed sequences for these purposes as well.

Response to Arguments

Applicant's arguments filed 5/13/04have been fully considered but they are not persuasive.

Applicant's arguments are presented at pages 8-11 of the response. Although the arguments at pages 10 and 11 are directed to a non-elected invention, they have

been considered to the extent that they apply to the rejection. The Applicant argues essentially that in order to make and use the claimed invention, it is not necessary to know the relationship between OA and the claimed polynucleotides. Applicant also argues at pages 10 and 11 that it would not take undue experimentation for one of skill in the art to determine what is the threshold level of SEQ ID NO:58 expression that is diagnostic of OA. This argument is unpersuasive because it assumes that a reliable correlation has been established between SEQ ID NO:58 and OA. While the specification indicates at page 71, lines 10-16 that SEQ ID NO: 58 is "upregulated as a result of OA", the objective truth of this statement is questionable in view of how "upregulated" sequences were identified. The specification teaches that 3 EST libraries were generated from 6 different OA donors (5 cartilage donors and one synovium donor), and were compared to two libraries generated from 5 non-OA donors (4 cartilage donors and one synovium donor). It is unclear how the comparison was made, and the relative contributions of the donors is unknown, as is the genetic background of each contributor. Absent this information, one cannot conclude that there is any significant correlation between SEQ ID NO:58 and OA, particularly in view of Fannon's teaching that the identification of potential diagnostic tools requires carefully constructed EST databases that can be viewed as a statistical sampling of genes expressed in disease states. As noted above, Fannon also indicates that such databases facilitate the identification of **candidates** that must subsequently be subjected to more rigorous characterization. See page 295, column 1, first two paragraphs. Finally, Applicant's argument that it would not take undue experimentation

to determine what is the threshold level of SEQ ID NO:58 expression that is diagnostic of OA is unpersuasive because it is simply a statement of opinion unsupported by factual evidence, and because MPEP 608.01(p) states that "[w]hile the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." In this case, the prior art provides no guidance with regard to using SEQ ID NO:58 to diagnose OA, so the burden of providing guidance in this regard falls solely on the specification. However, the specification provides no specific guidance as to what amount of SEQ ID NO:58 expression is considered to be diagnostic.

At page 9, Applicant states that it is not necessary to assess critical variables related to the preparation of the libraries. The Office notes that this alone might not be sufficient to result in a failure to enable the specification. However, inasmuch as it interferes with the ability of one of skill in the art to evaluate the assertion in the specification that SEQ ID NO:58 is upregulated in OA, it interferes with the use of the invention as intended as a diagnostic probe. The teachings of Fannon show that, in the absence of detailed information regarding the construction of libraries, the use of data mining to identify candidate genes is highly unpredictable. In view of the small sample size, and the uncertain nature of the library composition, it is extremely unpredictable as to whether the instant sample is statistically significant and contains a representative sample of gene expression. As a result, one of skill in the art would have to perform further experimentation in order to demonstrate a significant correlation between SEQ

ID NO:58 and OA, and to determine what, if any, level of expression was diagnostic of OA. In view of the state of the art data mining of ESTs, the unpredictability of drawing conclusions based on sample sizes of unknown statistical significance, and the lack of guidance and working examples in the specification, such experimentation is undue.

Applicant also argues at page 10 that it is not possible, or required for patentability, to establish a perfect correlation between expression and a disease profile. The Office notes that the rejection does not state any requirement for perfect correlation, instead the rejection points out the total lack of any guidance regarding what expression level of SEQ ID NO:58 is considered to be diagnostic of OA. The specification provides no guidance at all as to what level of OA is considered to be normal in any individual, nor what level of expression occurred in any of the diseased individuals who provided material for the libraries. This is critical information without which one of skill in the art cannot use the claimed nucleic acid for its intended purpose to diagnose OA. Failure to provide such critical information results in a failure to meet the enablement requirement. See MPEP 608.01(p). Applicant indicates that Fannon provides evidence in case studies on page 297 that experimentation with bioinformatic factors to correlate expression with disease profiles is routine. A review of these studies shows that they are intended to show only that "medically relevant genes" can be identified by database searching, and provide no support for the position that it is routine in the art to determine the level of gene expression that is diagnostic of a disease. Also, unlike the instant disclosure, the cited case studies disclose the frequency of occurrence of the candidate ESTs in target tissue and control tissue, as

well as the number of clones screened, such that one of skill in the art can draw a conclusion as to the significance of the data. However, because the case studies provide no guidance as to what level of expression of any of the identified ESTs is indicative of disease, they provide no support for the position that it is routine to determine such levels in general, or for SEQ ID NO:58 in particular. Applicant's statement at page 10 of the response that one of ordinary skill in the art would appreciate the correlation of up or down-regulated expression to the probability of developing OA is unpersuasive because it is unsupported by evidence and it presumes a significant correlation between SEQ ID NO:58 and OA that has not yet been demonstrated. For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.